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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/840,787	04/23/2001	Preeti Lal	PF-0356-3 DIV	5251

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EXAMINER
SLOBODYANSKY, ELIZABETH

ART UNIT	PAPER NUMBER
1652	17

DATE MAILED: 03/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/840,787	LAL ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-14 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-14,21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

The request for a continued prosecution application (CPA) under 37 CFR 1.53(d) filed on [1] is acknowledged. 37 CFR 1.53(d)(1) was amended to provide that the prior application of a CPA must be: (1) a utility or plant application that was filed under 35 U.S.C. 111(a) before May 29, 2000, (2) a design application, or (3) the national stage of an international application that was filed under 35 U.S.C. 363 before May 29, 2000. See *Changes to Application Examination and Provisional Application Practice*, interim rule, 65 *Fed. Reg.* 14865, 14872 (Mar. 20, 2000), 1233 *Off. Gaz. Pat. Office* 47, 52 (Apr. 11, 2000). Since a CPA of this application is not permitted under 37 CFR 1.53(d)(1), the improper request for a CPA is being treated as a request for continued examination of this application under 37 CFR 1.114. *See id.* at 14866, 1233 *Off. Gaz. Pat. Office* at 48.

Applicants Remarks filed December 9, 2002 have been entered.

The Declaration under 37 CFR 1.132 of Dr. Tod Bedilion filed on December 9, 2002 has been entered.

Claims 2-14 and 21 are pending.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 2-14 and 21 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility, credible asserted utility or a well established utility.

Applicants disclose a nucleic acid sequences (SEQ ID NO: 68) encoding the amino acid sequence of SEQ ID NO: 19 (HRM-19). The specification teaches that SEQ ID NO:19 that is 351 amino acids in length and has one potential mitochondrial motif, P_{31}LDVVKVRL. It further discloses that HRM-19 has sequence homology with C. *elegans* C16C10 (g577542) and is found in cDNA libraries associated with cell proliferation, cancer and immune response (page 18, lines 24-28).

The specification describes generic utility for polynucleotides as being part of microarrays (page 49, line 15, through page 51, line 7). The specification discloses that "polynucleotides used in the microarray may be oligonucleotides that are specific to a gene or genes of interest in which at least a fragment of the sequence is known or that are specific to one or more unidentified cDNAs which are common to a particular cell or tissue type or to a normal, developmental, or disease state" (page 49, line 30, through page 50, line 1, emphasis added). A DNA encoding SEQ ID NO: 19 does not meet

these requirements in that the specification does not teach that a DNA encoding SEQ ID NO: 19 is specific to a gene of interest or is "specific to one or more unidentified cDNAs which are common to a particular cell or tissue type or to a normal, developmental, or disease state".

Four years after the effective filing date of the application, Yu et al. (2001) (cited on form PTO-892 mailed September 12, 2002) disclose that while present in mitochondria, the function of CGI-69, one of the isoform of which is identical to HRM-19, is unknown (abstract, pages 371-372). They teach that CGI-69 does not posses properties common to mitochondrial carrier proteins and that "the unique carrier CGI-69 does not posses uncoupling behavior, but rather serves a different physiological role in mitochondria (page 374, 2nd column).

Therefore, while HRM-19 is a mitochondrial protein, one of ordinary skill in the art would not know its function except that it is not common to mitochondrial carrier proteins. Even if this protein is a mitochondrial carrier protein, one of ordinary skill in the art would not know which compound is a substrate for the carrier. Humans produce many mitochondrial carriers and each mitochondrial carrier is expected to have a specific substrate(s) and function. The art teaches that there are many mitochondrial carriers that import various metabolites, nucleotides, cofactors and compounds which are not synthesized in mitochondria (Palmieri, pages 48 and 49, cited on form PTO-892 mailed May 1, 2002).

Therefore, as disclosed, a protein of SEQ ID NO:19 is an uncharacterized protein with no known function.

Furthermore, for a method of detection of a nucleic acid in a sample to be useful, one must know the biological significance of the polypeptide(s) which is(are) being detected. Without this information, the results of the expression profile are useless because one would not know if the polypeptide expression should be increased or decreased or even what significance could be attributed to such changes in expression profiles. Without this knowledge, which could not be gleaned from the instant specification as filed, one of ordinary skill in the art at the time the instant invention was made would not have been able to use the information obtained from an expression profile in a useful manner. There is no evidence to the contrary.

Claims 13, 21 and 14 are drawn to a method for diagnosing an unspecified disease and lung cancer, respectively.

Neither the specification nor the art of record disclose any specific disease or conditions that can be diagnosed using a DNA encoding SEQ ID NO:19.There is no indication that increasing or decreasing the expression of HRM-19 would have any use in diagnosing any diseases. Therefore, diagnosing of an unspecified, undisclosed disease or condition or cancer or immune response would require or constitute carrying out further research to identify or reasonably confirm a disease that can be diagnosed using a DNA encoding SEQ ID NO:19. With regard to diagnosis of disease, in order for

a polynucleotide to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polypeptide and a disease or disorder. The presence of a polypeptide/polynucleotide in tissue that is derived from some cancer cells is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed polypeptide and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polynucleotide is either present only in cancer tissue to the exclusion of normal tissue or is expressed in higher levels in a specific diseased tissue compared to normal tissue (i.e. overexpression). Evidence of a differential expression might serve as a basis for use of the claimed polynucleotide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polynucleotide and any disease or disorder and the lack of any correlation between the claimed polynucleotide with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself.

Therefore, it appears that the main utility of the polypeptide and nucleic acid is to carry out further research to identify the biological function and possible diseases associated with said function. Substantial utility defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utility. In view of the above, a DNA encoding SEQ ID NO:19 and methods of use thereof have no specific, substantial, credible and well-established utility.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-14 and 21 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Response to Arguments

Applicant's arguments filed December 9, 2002 have been fully considered but they are not persuasive.

Applicants argue that utility of a gene encoding SEQ ID NO:19 is based on the fact that it "is expressed in humans. The novel polynucleotide codes fro a polypeptide demonstrated in the present specification to be a member of the class of mitochondrial carrier proteins, whose biological functions include transport of ions and charged metabolites between the cytosol and the mitochondrial matrix. As known in the art at the time of filing, alterations in the mitochondrial electron transport chain are characteristic of malignant cells (Tab I, p.343), and mitochondria were also known to have a central role in regulation of apoptosis, an important contributor to cancer and other cell proliferative disorders (Tab. J, pp. 34-35). As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the polynucleotide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success" (Remarks, page 4). This is not agreed with because the present specification did not demonstrate the function of HRM-19 in mitochondria and, if it is a member of the class of mitochondrial carrier proteins, the specification did not demonstrate its substrate specificity, i.e. what it specifically carries. Further, alterations in the mitochondrial electron transport chain can be observed in non-malignant cells and said alterations, if and when they exist, are not the only alterations that render a cell malignant. The same is relevant to apoptosis which occurs in both normal and cancer cells. Furthermore, the specification

lacks any mentioning of toxicology testing and Applicants did not provide evidence of commercial success based on the claimed invention. While toxicology testing may be known in the art at the time of filing, as an essential element, it should be described in the specification.

Applicants argue that "its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight" (sentence bridging pages 9 and 10). The examiner disagrees with that analogy because this analogy is fair with regard to scales and microarrays in general. In general, microarrays comprising useful polynucleotides are useful. However, it is not analogous to a microarray which utility is based on the nucleotide of the instant invention. In other words, the addition of a DNA encoding SEQ ID NO:19 to a microarray does not impart the utility if the microarray did not have one. On other hand, the scales are used when there is a reason for the importance of measuring weight. For example, to monitor whether the treatment prevents the weight loss of a cancer patient. The scales invented only to measure weight of something for what the importance of weight is not known are not useful. If a DNA encoding SEQ ID NO:19 would be known to encode a specific function or to be differentially expressed in particular tissues or in certain physiological or pathological conditions, a microarray comprising it would have utility based on that.

Applicants further compare their invention to research tools "MPEP § 2107 ("Many research tools such as gas chromotographs, screening assays, and nucleotide

sequencing techniques have a clear, specific, and unquestionable utility (e.g., they are useful in analyzing compounds)" (emphasis added))" (page 10, 1st paragraph). For the reasons stated above, Applicants do not explain how to analyze compounds using a polynucleotide encoding SEQ ID NO:19.

Furthermore, MPEP § 2107.01 states that "a claim to a polynucleotide whose use is disclosed simply as a "gene probe: or "chromosome marker" would not be considered to be *specific* in the absence of a disclosure of a specific DNA target. A general statement of diagnostic utility such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed" (emphasis added). For the reasons discussed above, the examiner considers said guidelines directly analogous to the instant invention.

Applicants further refer to the Bedilion Declaration for showing "that a number of pre-September 23, 1997 publications confirm and further establish the utility of cDNA microarrays in a wide range of drug development gene expression monitoring applications at the time the Lal '750 application was filed (Bedilion Declaration 10-14; Bedilion Exhibits A-G))" (page 10). The examiner does not argue the utility of cDNA microarrays in general and, specifically, the utility of the whole genome microarrays to which Applicants refer on page 12. Applicants further argue usefulness of DNA arrays in toxicology (page 13). The importance of toxicology testing and the use of DNA arrays therefor is unquestionable. What is not agreed with is the usefulness of a microarray

comprising a DNA encoding SEQ ID NO:19 if the same microarray without it did not have utility. For the same reasons, examples of benefits presented on page 14 are not persuasive because they attest to the usefulness of databases that do not comprise a gene of the instant invention but other DNAs that represent genes of interest.

Applicants further argue that "the fact that the claimed polynucleotide encodes a protein in the mitochondrial carrier protein family also demonstrates utility" (page 14 and in discussion on pages 15-19). Applicants disagree with the examiner's position presented above stating that "while these "general classes" may contain a substantial number of useless members, the mitochondrial carrier protein family does not. The mitochondrial carrier protein family is sufficiently specific to rule out any reasonable possibility that HRM-19 would not also be useful like the other members of the family" (page 19, emphasis added). However, as shown by Yu et al., *supra*, HRM-19 is not "like the other members of the family". It is agreed that carrier proteins for which their function is known are useful. However, even if HRM-19 is a carrier protein it would require carrying out further research to identify its unique function. Applicants argue that because HRM-19 is naturally-occurring, it must be "pre-selected by nature to be useful" (page 19). However, the researcher has to carry out further undisclosed experiments to find out in which way the nature made HRM-19 useful. As discussed above, Yu et al., *supra*, refers to the protein as uncharacterized protein and demonstrates that it "does not posses uncoupling behavior, but rather serves a different

physiological role in mitochondria" (abstract, page 371, 1st column, page 374, 2nd column, emphasis added). Yu et al. suggest further research to elucidate said role (page 374). Without knowing how HRM-19 functions in mitochondria, its utility remains unknown.

Applicants further refer to the issues discussed in the Declaration of Preeti Lal field September 3, 2002 and addressed in the Final Office action mailed September 12, 2002. Applicants state that "evidence provided in the Lal Declaration, such as the Yu article which provides experimental evidence that HRM-19 is a mitochondrial carrier protein, serve to **confirm** what was previously asserted" (page 22). As stated in the Final Office action "Applicants argue with the support of the Declaration that the gene encoding SEQ ID NO:19 is up-regulated in lung cancer (Remarks, page 5; [Lal] Declaration, Exhibit D). Regardless of whether these data can provide the support for the utility, said utility is not described in the specification, i.e., there is no mentioning that the gene encoding SEQ ID NO:19 is up-regulated in lung cancer. The specification provides no specific teaching regarding HRM-19 but only the teaching regarding all HRM in general. It teaches that "polynucleotides encoding HRM may be used for the diagnosis" of various diseases of a non-discriminatory list of all human organs (emphasis added, specification, page 47, line 24 through page 48, line 24)" (Final Office action, page 8). The specification does not disclose that HRM-19 is differentially expressed in any tissues or in any conditions. Moreover, there is no reason for one of

ordinary skill in the art to specifically select lung tissue and not synovial tissue, for example, from which library HRM-19 was identified (specification, page 18, lines 20-21).

Dr. Bedilion's Declaration attests to the usefulness of microarrays in toxicology testing. These issues were addressed above in response to Remarks. The examiner notes that the publications referred to in the declaration have been never mentioned in the specification or supplied with IDS. Dr. Bedilion refers to articles by Heller et al. and Biswas et al., for example, to support the utility of any microarray comprising any expressed polynucleotide. However, both articles teach specific design for microarrays. Heller et al. teach that "two approaches for the fabrication of c DNA microarrays were use in this study. In the first approach, known human genes of probable importance in RA were identified. ... In the second approach, the microarray containing the 1056 human genes from the peripheral blood lymphocyte library was prepared" (Heller et al., paragraph bridging pages 2150-2151, emphasis added). As mentioned above, in the instant case, the important of HRM-19 gene is unknown and one of ordinary skill in the art would not have known what particular cells to choose. Applicants refer to Biswas et al. to teach that "alterations in the mitochondrial electron transport chain are characteristic of malignant cells (Tab. I, p.343)" (Bedilion's Declaration, page 14, lines 1-2). However, as shown by Yu et al. and discussed above, HRM-19 is a unique mitochondrial protein that does not share the uncoupling ability with other carriers and

therefore, probably does not participate in the mitochondrial electron transport chain, and would not be useful to study this aspect of malignancy.

Dr. Bedilion repeatedly states that "microarray that contained the SEQ ID NO:19-encoding polynucleotides would be a more useful tool than cDNA microarrays that do not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs from treating cell proliferative disorders for such purposes as evaluating their efficacy and toxicity" (Declaration, page 11). For the reasons given above, this is not persuasive.

Therefore, the utility for a DNA encoding SEQ ID NO:19 is not established because the following is not shown: a) the function of HRM-19 in mitochondria or b) its differential expression in a particular cell or condition.

Conclusion

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner

February 28, 2003